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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/521,742	03/09/2000	Lars Hammarstrom	49122	2762

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EXAMINER
HARRIS, ALANA M

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 03/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/521,742	HAMMARSTROM ET AL.	
	Examiner	Art Unit	
	Alana M. Harris, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-57* is/are pending in the application.

4a) Of the above claim(s) *1-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Prosecution Application

1. The request filed on December 12, 2002 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/521,742 is acceptable and a CPA has been established. An action on the CPA follows.

2. Claims 1-57 are pending.

Claim 28 has been amended.

Claims 47-57 have been added.

Claims 1-27, drawn to non-elected inventions are withdrawn from examination.

Claims 28-57 are examined on the merits.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 28-57 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating malignant cancer cell lines (such as those listed in Table 1 of the specification, see page 26) by contacting the said cells with an enamel matrix derivative, namely EMDOGAIN® thereby inducing apoptosis, does not reasonably provide enablement for a method for treating epithelially/ectodermally derived benign, semi-malignant or malignant, comprising

administering to a mammal an active enamel substance. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

In anticipation of the instant rejection Applicants argue that the description of the claimed invention has been "...provided in sufficient detail to render a person skilled in the art able to practice and implement such treatment commensurate in scope with the claimed invention without undue experimentation." Applicants set forth that the claimed invention encompasses the topical administration of a therapeutically effective amount of an active enamel substance for treatment of mammalian ectodermally derived neoplasms or neoplastic cells and not all benign or malignant neoplasms. Applicants further submit that the specification provides "...several examples of suitable proteins for use in accordance with the present invention...with particularity." These arguments have been carefully considered but found unpersuasive.

Applicants' claims read on the broad treatment of numerous epithelially derived benign, semi-malignant or malignant neoplasms with a therapeutically effective amount of an active enamel substance, which is not defined by the claims. The said neoplasms originate from several organ systems, such as glandular, bone, skin, ovarian and muscle tissue. Applicants have not provided any enabling disclosure supporting the use of active enamel substances as effective pharmacological agents in methods of direct mammalian treatment. Furthermore, the said substances have not been clearly defined. Applicants' specification suggest that active enamel substances include enamelins, amelogenins, non-amelogenins, as well as a host of other enamel

derivatives, matrix, substances, see page 1, lines 25-32; page 5, line 33-page 10, line 7; and page 7,lines 1-8. These substances purportedly are effective in inducing apoptosis in neoplastic cells. What remains questionable is the identity of which substances should be considered derivatives capable of inducing apoptosis. It is not clear if enamel substances, such as proline-rich non-amelogenins and tuftelins mixed together in undefined proportions be expected to act in the same manner yielding the same result being apoptosis. Applicants' specification has not evidenced the use of possible enamel derivative combinations in a method for treating epithelially derived malignant or benign neoplasms *in vivo* or *in vitro*.

Granted the Office does not require that experiments under the scope of the claims produce positive and astonishing results, the experiments must be within the scope of the Forman factors (see Ex parte Forman, 230 USPQ 546, BPAI, 1986). Applicants have not provided any objective evidence (particularly *in vivo*, which the claims encompass) or data that supports the administration of active enamel substances. The information provided in the specification is not substantive enough to support the claimed invention's effectiveness as a therapeutic.

The specification has only provided evidence of treating cell lines from specified organ systems such as the mammary glands and skin, see page 26. One skilled in the art could not be expected to identify all cell types from any and all neoplasms that are at least responsive to any active enamel substance, derivatives or mixtures. There would also need to be some valid amount of direction or guidance, as well as presence or absence of working examples presented in the specification that would enable one

skilled in the art to perform the method as presented in the recited claims. The predictability of the art in regards to the correlation of *in vivo* experimentation with *in vivo* experimentation is insurmountable.

There is no guidance on the pharmacokinetics regarding any and all active enamel substances to be administered which is necessary for one of skill in the art to practice the invention in order to achieve predictable results. With regard to the results, in general, treatment of cancer is at most unpredictable as underscored by Gura (Science 278: 1041 and 1042, November 7, 1997) who discusses the potential shortcomings of potential anti-cancer agents including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice- particularly strains which have tumor suppressor gene knockouts, and problems of clonogenic assays. Indeed, since formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041, 1st column) wherein the fundamental problem in drug discovery for cancer is that the model systems are not predictive. The greatly increased complexity of the *in vivo* environment as compared to the very narrowly defined and controlled conditions of an *in vitro* assay does not permit a single extrapolation of an *in vitro* assay to human therapeutic efficacy with any reasonable degree of predictability. *In vitro* assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Further a therapeutic agent must accomplish several tasks to be effective: interact at the proper site of action, and it must do so at a therapeutic concentration and remain effective for a

sufficient period of time. *In vitro* assays cannot duplicate the complex conditions of *in vivo* therapy.

Due to the unpredictability of therapeutics, the absence of any evidence concerning the effectiveness of the undefined composition comprising a plethora of enamel substances as a pharmacological agent, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the claimed invention with a reasonable expectation of success. The quantity of experimentation necessary to determine whether or not any active enamel substance is capable of preventing or treating any malignant or benign neoplasms is infinite.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 28-57 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In anticipation of the instant rejection "Applicants submit that the noted claims are abundantly clear and definite when read in view of the supporting specification." This is not found persuasive.

a. The recitation " therapeutically effective amount of an active enamel substance" in claims 28-41, 43, 47, 48 and 52-57 are vague and indefinite. It is not clear what amount is considered an effective amount and how it is considered therapeutic. Furthermore, it is not clear if therapeutic amount is to result in just

treatment, remediating, or curing. Accordingly, the metes and bounds cannot be determined. The claims containing this recitation must be definite as to allow the comparison with the available art and clear for the public to determine what the claims encompass. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims.

b. Claims 30, 30 and 46 are vague and indefinite in the recitations " enamel matrix derivatives", "derivatives thereof" and "mixtures thereof". Applicants have not set forth specific combinations of all the enamel substances, combinations, percentages of the different substances that comprise the derivatives and mixtures. Hence the metes and the bounds of the claims cannot be determined. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims.

c. Claim 50 is vague and indefinite because it does not end with a period. Accordingly, it is not clear what other text is missing from the claim.

7. Claims 28-57 are free of the art.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alana M. Harris, Ph.D. whose telephone number is (703) 306-5880. The examiner can normally be reached on 6:30 am to 4:00 pm, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4315 for regular communications and (703) 308-4315 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

ALANA HARRIS
PATENT EXAMINER

Alana M. Harris, Ph.D.
March 20, 2003